Why Nano?

In supporting the National Cancer Institute's mission, few areas of research are poised to make as big a contribution as cancer nanotechnology. Already, the marriage of cancer biology and nanotechnology is generating revolutionary methods for detecting and treating cancer that are on the path to clinical use. Already, nanotechnology has yielded new tools that are accelerating the pace of discovery from our nation's cancer centers and research laboratories. Already, this science of the very small is attracting the brightest researchers from a wide variety of scientific and engineering disciplines to bring their talents to bear on the problems of transforming cutting edge research into clinical advances.

"The application of nanotechnology to cancer research could not come at a more opportune time given the recent exponential increase in our understanding of the process of how cancer develops," says Andrew von Eschenbach, M.D., director of the National Cancer Institute. "It is my belief that nanomaterials and nanodevices will play a critical and unique role in turning that knowledge into clinically useful advances that detect and interact with the cancer cell and its surroundings early in this process. By doing so, we will change for the better the way we diagnose, treat, and ultimately prevent cancer."

An example can serve to highlight the enormous potential of cancer nanotechnology for changing the detection and therapy paradigm. Paras Prasad, Ph.D., a professor of chemistry at the University of Buffalo, and Raoul Kopelman, Ph.D., a professor of chemistry, physics, and applied physics at the University of Michigan, have developed nanoparticles—imagine tennis balls 1/10,000th the size of the head of a pin—that can detect tiny tumors in a living animal and at the same time deliver potent, light-activated cell killers just to the tumors whose location they've just pinpointed.

But that's not all. Once these nanoparticles have arrived at the tumors, and the drugs inside of them are activated using tiny fiber optic lasers, the nanoparticles can then reveal if the therapy is actually killing cancer cells. "The idea that the same single injection of an agent can detect, treat and report on the success of therapy is something that only nanotechnology can achieve," says Dr. Kopelman.

This is NOT a new science—and that's good

Today, the work of researchers such as Dr. Kopelman and Dr. Prasad have made nanotechnology a hot topic, the subject of increasing public attention and news coverage. Some may look upon this newfound attention as just the latest example of "the next hot thing," another dot.com bubble in the making. But what's unusual about all of this nanotechnology hoopla is that it is actually late in coming, because the fact of the matter is that chemists, physicists, engineers and biologists have been engaged, quietly, in nanotechnology research long before anyone even thought about the word nanotechnology. Dr. Kopelman's work, for example, has received NCI support, through the Unconventional Innovations Program, since 2000.

In fact, many chemists and biologists argue that they have been working at the nanoscale—the realm that stretches from 1-100 nanometers in length—since the early days of the 20th century. A typical protein such as hemoglobin, which carries oxygen through the bloodstream, is 5 nanometers, 5 billionths of a meter, in diameter. Most drug molecules are actually smaller than a nanometer, while the atoms of silicon that make up a computer chip are spaced about 1/10th of a nanometer apart.

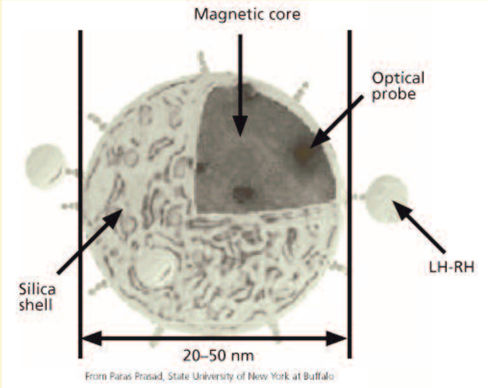
But working with and studying atoms and molecules, proteins and DNA, in general, are not what researchers refer to when they talk about nanotechnology. While many definitions of nanotechnology exist, most experts follow the lead of the U.S. National Nanotechnology Initiative (NNI)'s definition, which refers to nanotechnology as the field of science that involves all of the following:

- Research and technology development at the atomic, molecular or macromolecular levels, in the length scale of approximately 1-100 nanometer range.
- Creating and using structures, devices and systems that have novel properties and functions because of their small and/or intermediate size.
- Ability to control or manipulate on the atomic scale.

Based on this definition, the birth of nanotechnology can be traced to 1985 and two developments that each led to Nobel Prizes. The first took place at IBM Research in Zurich, Switzerland, where physicists Gerd Binnig, Ph.D., and Heinrich Rohrer, Ph.D., invented the scanning tunneling microscope (STM), which for the first time gave scientists the ability to see individual atoms in a material and move them around, atom by atom. The pair of physicists first published their work in 1985 and were awarded the Nobel Prize in Physics in 1986.

The second development took place over the course of 11 days in 1985 at Rice University when chemists Robert Curl Jr., Ph.D., Richard Smalley, Ph.D., and Harold Kroto, Ph.D., who was visiting from the University of Sussex in England, created a

Courtesy: Paras Prasad, Ph.D., University of Buffalo



Multifunctional nanoparticles can be targeted to cancer cells using receptor ligands.

new form of carbon, which they named buckminsterfullerene and that we now call buckyballs for short. Unlike the other forms of carbon that contain a virtually unlimited number of carbon atoms—sheet-like graphite and crystalline diamond being the two most well-known examples—buckyballs were made of a finite number of carbon atoms, 60 to be exact, that formed a spherical shape exactly like that of a soccer ball and the geodesic structure invented by the architect Buckminster Fuller. Their findings were controversial, and the ensuing efforts to characterize these new nanoparticles not only won the trio the 1996 Nobel Prize in Chemistry, but started an avalanche of research into nanoscale materials.

Coincidentally, the birth of cancer nanotechnology can be traced to about the same time, though this research was less concerned about the fundamental nature of matter and more concerned with the question of how to save lives. In the mid-1980s, Jill Adler-Moore, Ph.D., a microbiologist at California State Polytechnic University in Pomona, and Richard Proffitt, Ph.D., who was at the biotech firm Vestar (now part of Gilead Sciences), created nanoscale fatty spheres known as liposomes containing the potent but incredibly toxic antifungal drug amphotericin B. This new formulation of an old drug was taken up by immune system cells called macrophages and delivered to the very sites at which fungi were growing in the human body. Equally important, the liposomes kept amphotericin B away from sensitive kidney cells. The result was a drug that physicians could now use safely—and at much higher doses—to successfully treat life-threatening fungal infections that often develop in cancer patients who have received bone marrow transplants. Soon afterwards, other researchers developed liposomes that could more safely and effectively deliver the anticancer agent doxorubicin to tumors.

The Promise of Nanotechnology Today

Though there have been few nanoscale products to reach human clinical use since those initial liposomal products, that does not mean that cancer nanotechnology reached a dead end. Rather, chemists, engineers and biologists have spent the past two decades mastering the intricacies of working with materials at the nanoscale. The result is that researchers now have a much clearer picture of how to create nanoscale materials with the properties needed for effective use in humans.

"Working at the nanoscale proved to be more difficult than we might have thought based on the early successes with liposomes," said Mauro Ferrari, Ph.D., a professor at Ohio State University who spent two years helping the NCI develop the Alliance for Nanotechnology in Cancer Initiative. "But today, with the wide range of nanoscale materials that we now have at our disposal, the potential applications are limited not so much by chemistry or engineering, but by our imagination and our knowledge of cancer biology."

Cancer nanotechnology encompasses a wide range of materials and techniques being applied to a wide range of problems, including:

- Early imaging agents and diagnostics that will allow clinicians to detect cancer in its earliest, most easily treatable, presymptomatic stage;
- Systems that will provide real-time assessments of therapeutic and surgical efficacy for accelerating clinical translation;
- Multifunctional, targeted devices capable of bypassing biological barriers to deliver multiple therapeutic agents at high local concentrations, with physiologically appropriate timing, directly to cancer cells and those tissues in the microenvironment that play a critical role in the growth and metastasis of cancer;
- Agents capable of monitoring predictive molecular changes and preventing precancerous cells from becoming malignant;
- Surveillance systems that will detect mutations that may trigger the cancer process and genetic markers that indicate a predisposition for cancer;
- Novel methods for managing the symptoms of cancer that adversely impact quality of life; and
- Research tools that will enable investigators to quickly identify new targets for clinical development and predict drug resistance.

Nanoparticles, of which there are many different types, will certainly play a major role in bringing each of the applications to life. Though the specific properties of each nanoparticle may differ, and though each investigator has his or her own approach to using nanoparticles for developing new methods for cancer detection and treatment, there are a few fundamental characteristics that tie all of these efforts together and generate excitement across the field of cancer nanotechnology. To begin with, researchers have designed nanoparticles so that it is relatively easy to attach dozens to thousands of molecules to the surface of the particles. These molecules can be drugs or imaging agents, but perhaps most importantly, they can be molecules that target the particles to tumors, a molecular address, so to speak.

One common targeting agent, for example, is the molecule folic acid (also called folate), which recognizes and binds to a folate receptor that is found on certain types of cancer cells. Other targeting agents include an antibody that recognizes and binds to a protein known as Her-2, which is found on the cells of certain types of breast cancer, and an aptamer (a piece of nucleic acid that acts like a supercharged antibody) that binds to prostate specific antigen, found on prostate cancers. Cancer biologists are constantly looking for and finding such cell surface markers and when they do, cancer nanotechnologists add them to their tool box of targeting agents.

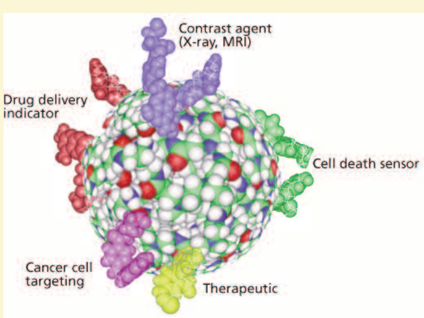
At this point, you might ask why chemists don't just attach a targeting agent directly to a drug molecule or imaging agent and skip the added complexity of using a nanoparticle. That's a good question, and it is something that pharmaceutical chemists have tried, but nanoparticles offer two big advantages. The first has to do with the way that a targeting agent and its target stick to one another. When folic acid binds to the folate receptor, it sticks to its receptor for some finite time and then comes off and moves on, perhaps to another nearby folate receptor on the same cell, perhaps not. Now think about the way that the hook and loops of Velcro work to hold two objects together and that will give you an idea of how a nanoparticle with dozens of targeting molecules can stick to its target more tightly than a drug molecule attached to one targeting molecule. "Every time one targeting agent comes off its receptor on the cancer cell, you still have many others still stuck to their receptors on the same cell," says Gregory Lanza, M.D., a professor of medicine at Washington University in St. Louis who has been developing targeted nanoparticles with funding from the NCI's Unconventional Innovations Program.

The second reason why a targeting agent-nanoparticle combination is a better bet for finding or killing cancer cells is a much simpler one—unlike a drug molecule or imaging agent, which is a discrete chemical, a nanoparticle is essentially a large container that can be loaded with tens of thousands of imaging agent or drug molecules. "Using a nanoparticle instead of a single drug molecule is like delivering a huge parcel compared to a post card," explains Dr. Kopelman.

Loading a targeted nanoparticle with drug can also greatly reduce the toxicity associated with many cancer drugs. Targeting, by its very nature, sends more drug to a tumor and less drug to healthy tissue, and that effect alone can cut down on adverse side effects while boosting a drug's effectiveness.

Nanoparticles, targeted or not, can also reduce side effects by eliminating the need for various chemicals that are sometimes added to drug formulation in order to render the active ingredient soluble in the body's fluids. A prime example is the recently approved drug Abraxane™, a nanoparticle formulation of the potent anticancer drug paclitaxel. As the active ingredient in Taxol®, paclitaxel has become a major weapon in the oncologist's armamentarium, but paclitaxel is poorly soluble in biological fluids. To overcome this solubility problem, pharmaceutical chemists had to resort to mixing paclitaxel with various chemicals that often produced dose-limiting side effects. Loading paclitaxel into a nanoparticle made of albumin, a major blood protein, eliminated the need for these extra chemicals with the result that patients could be given far higher doses of paclitaxel with far fewer side effects.

Courtesy: James Baker Jr., M.D., University of Michigan



Dendrimers can serve as versatile nanoscale platforms for creating multifunctional devices capable of detecting cancer and delivering drugs.

Multi-tasking in a nanoparticle

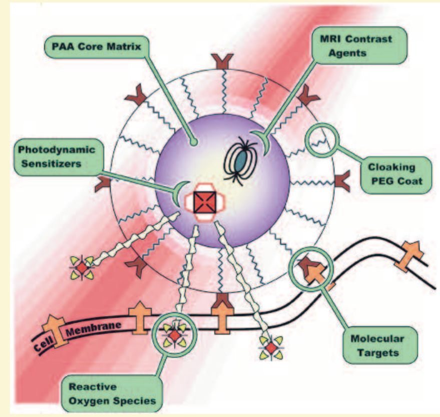
One of the most promising uses of nanoparticles is to use them to simultaneously image a tumor and deliver anticancer agents to the tumor. Drs. Kopelman, Prasad and Lanza are all working on such applications, as is James Baker Jr., M.D., whose work has also been supported by NCI. Dr. Baker's group at the University of Michigan has been developing multifunctional dendrimers, which are spherical, nanometer-sized polymer particles that can be decorated with a wide variety of molecules. In recent months, his group has published papers showing that targeted multifunctional dendrimers can both image and kill tumors in laboratory animals.

The pages of Nano.Cancer.Gov have highlighted other multifunctional nanoparticles that are making their way toward human clinical testing. Such multifunctionality is perhaps the most revolutionary characteristic that nanoparticles bring to cancer researchers. "It's not just that we can image a tumor and then dose it with a drug," says Dr. Prasad, "but that we have the potential to dose a tumor not just with one drug, but many drugs simultaneously. We can attack multiple pathways, multiple targets at the same time and greatly increase the odds of killing all the cells in a tumor."

Such a multi-pronged attack could solve one of the most vexing problems facing cancer patients—drug resistance. In most cases, drug resistance occurs when a cancer cell acquires the ability to pump drugs out as fast as they enter a cell. But imagine a nanoparticle loaded with a pump inhibitor and a slew of toxic chemicals, all targeted to a malignant cell. "That's where the real power of nanotechnology comes into play," adds Dr. Kopelman.

Besides detecting a tumor and dosing its cells with multiple anticancer agents, cancer researchers also hope to use nanoparticles to carry reporters with them that will signal when a therapy is actually working. "Having the means to see in real time if a therapy is working will have tremendous benefits for cancer patients," says Dr. Lanza. "Instead of waiting weeks or months to see the effects of a particular therapy, we will soon have the means of knowing within hours or days if the patient is going to respond positively."

Courtesy: Raoul Kopelman, Ph.D., University of Michigan



"Smart" dynamic nanoplatforms have the potential to change the way cancer is diagnosed, treated, and prevented. The outside of such "nanoclinics" could be decorated with a tumor-homing monoclonal antibody and coated with polyethylene glycol (PEG) to shield the device from immune system detection. The polymer matrix of such particles could be loaded with contrast agents, which would provide enhanced sensitivity for pinpointing tumor locations within the body, and various types of therapeutic agents, such as reactive oxygen-generating photodynamic sensitizers that would be activated once the particle detected a malignant cell.

Certainly, much work remains to create clinically useful nanoparticles that combine all of these properties—targeting, payload, multifunctionality, and the ability to overcome resistance—into one package. There are also concerns among researchers that regulatory agencies will balk at the notion of packaging more than one function into a nanoparticle for use in humans. Still, the mood among cancer nanotechnologists is optimistic that the technical and regulatory challenges will be overcome and that cancer nanotechnology will produce enormous benefits for cancer patients. "Nanotechnology gives us the opportunity to create new paradigms for treatment that I believe will ultimately turn cancer from something that we fear into a very manageable disease like high blood pressure," says Dr. Lanza.

—*Joe Alper*